

## Lack of Awareness of Dietary Sources of Phosphorus Is a Clinical Concern

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**Abstract.** *Hyperphosphatemia is a serious complication in patients with chronic kidney disease (CKD), and is associated with more rapid progression as well as higher risk of mortality, and higher rate of cardiovascular disease accidents. CKD patients are usually advised to adopt a low phosphate diet in addition to phosphate-lowering medications, if necessary. However, there is a lack of awareness of the dietary sources of phosphate, especially hidden phosphate intake from phosphate additives in processed foods and carbonated beverages. Appropriate nutritional education could be an effective solution in reducing phosphate toxicity without introducing an additional pill burden or malnutrition.*

Phosphate is an essential component of the human body (1), however, recent studies have shown the risk of excess phosphate intake in early aging, arteriosclerosis and renal diseases (2-4). In patients with chronic kidney disease (CKD), hyperphosphatemia is associated with higher risk of mortality (5, 6) and cardiovascular disease (CVD) which is the most common cause of death in CKD (7). Additionally, hyperphosphatemia has been suggested as being a risk factor for a more rapid progression of CKD (8). CKD patients are, therefore, advised to restrict dietary intake of phosphate, as well as take phosphate-lowering medications to maintain serum phosphate levels in the normal range (9, 10). Nevertheless, there has been a lack of interventional studies

demonstrating improved outcomes from restriction of dietary phosphate (11). In this review, we discuss the recent nutritional research related to phosphate toxicity.

### Phosphate Toxicity

*Risk of mortality, cardiovascular diseases and CKD progression.* Recent studies have revealed the risks of increased serum phosphate levels in aging, atherosclerosis and renal disease (2-4, 12, 13). Hyperphosphatemia is an independent risk for mortality and CVD in patients with CKD who are undergoing maintenance hemodialysis (5, 6). It is also related to mortality and the risk of CVD in non-dialysis CKD patients (7, 13). In addition, hyperphosphatemia is associated with a more rapid CKD progression (8). And furthermore, high-normal phosphate levels are also related to an increased risk of CVD (14), and coronary atherosclerosis (15) in patients with normal kidney function. However, the mechanisms of elevated risks associated with CVD-related hyperphosphatemia are not fully understood. Initially, secondary hyperparathyroidism followed by hyperphosphatemia was found to be associated with vascular calcification and myocardial hypertrophy as well as cardiac dysfunction (16). Recent evidence has demonstrated the role of hyperphosphatemia itself in vascular calcification and CKD-mineral bone disorder. Phosphorus toxicity is now considered to be the main cause of cardiovascular mortality (17), and, furthermore, it is also toxic to the endothelial cells of blood vessels (18). The increased serum phosphate from excessive consumption of dietary phosphate additives induces increased carotid intima-media thickness (19, 20). In addition, elevated dietary phosphate load can also increase fibroblast growth factor-23 (FGF-23) concentration, which has been linked to cardiac hypertrophy and adverse cardio-vascular outcomes (21-23).

*Possible effects of carbonated drinks on healthy adults with normal kidney function.* It is not yet known whether or not the phosphate in common foods and beverages influence

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individuals with normal renal function. In this study, we examined the effect of carbonated drinks in healthy volunteers. The subjects were 55 university students. Thirty-five of the students, whose average age was 21.2 years, drank 350 ml of carbonated soda and 20 of the students, whose average age was 19.9 years, drank 350 ml of mineral water. Urine samples were collected before and also 2 h after consumption. Urinary protein and glucose concentrations were determined qualitatively using test paper, while the amounts of urinary phosphate, calcium and creatinine were measured using an auto-analyzer. Urinary phosphate and calcium levels were normalized to creatinine concentration. The mean level of urinary calcium in these 35 volunteers increased significantly after consumption of the carbonated soda, while there was no change in urinary calcium excretion in the 20 control students, who drank water. A 350 ml portion of carbonated soda contains about 50 mg of phosphate and may enhance calcium excretion in normal individuals. This result suggests that a standard soda drink can even influence individuals with normal renal function (24). Moreover, dietary phosphorus overload may be related to various kinds of malignancies such as lung, breast and prostate cancers, since phosphorus burden influences cancer cell growth and metabolism (3, 25, 26). However, the results of earlier studies have not always been consistent and further research is needed to clarify the underlying molecular connections.

*Why does hyperphosphatemia occur in CKD?* Mechanism of hyperphosphatemia in CKD patients is summarized in Figure 1. Levels of serum phosphate are generally regulated by (i) dietary intake (ii) absorption in the intestine, and (iii) reabsorption by the proximal tubules (27). Since renal regulation is crucial in chronic renal insufficiency, reduced glomerular filtration rate (GFR) leads to phosphate retention. Serum phosphate is filtered through the glomerulus into urine and is reabsorbed by the NaPi-2 co-transporter in the proximal tubules (28). The amount of filtered phosphate decreases as glomerular function declines and so hyperphosphatemia is usually observed in various stages of disease of CKD patients and is always present in hemodialysis patients. Serum phosphate levels usually rise when GFR is below about 35 ml/min per 1.73 m<sup>2</sup> (29). Serum calcium levels are related to serum phosphate levels, and the mathematical product of serum phosphate and calcium is concentrations that are usually constant. Therefore, when serum phosphate levels rise, serum calcium levels fall. An injured kidney cannot activate vitamin D and low vitamin D levels lead to reduced calcium absorption in the intestine. The body tries to correct the low serum calcium levels by releasing parathyroid hormone (PTH) to raise serum calcium, which releases calcium from bones. As a result, bones become weak and sometimes bone pain can occur. Ectopic calcification is often observed in various human

organs, such as joints, sub-dermal soft tissue, conjunctiva membranes, lungs and arteries (30). Arterial calcification accelerates arteriosclerosis, while osteomalacia is a particularly serious problem in children of short stature (31).

Phosphate retention enhances the release of FGF-23 from bone (32). This FGF-23 functions in conjunction with the enzyme klotho in tubular cells to inhibit the reabsorption of phosphate in proximal tubules (33). FGF-23 also potently suppresses vitamin D activity, possibly to limit further gastrointestinal absorption of phosphate, resulting in diminished calcium absorption and further stimulation of PTH. Reduced renal function can no longer support further phosphate excretion, and serum PTH levels rise with this reduction, thus serum levels of phosphate increase further as renal function declines.

A high level of serum FGF-23 is the earliest marker of renal dysfunction rather than overt hyperphosphatemia itself (34). Recent studies have reported that serum FGF-23 levels anticipate congestive heart failure and are related to left ventricular hypertrophy (35, 36), making these levels an independent risk factor for CVD (32) and mortality (37). Thus, phosphate restriction may need to be initiated even earlier, so that FGF-23 can be maintained within normal limits.

Klotho is a single-pass transmembrane protein and is expressed in multiple tissues but its expression is particularly high in the kidney (33). It is strongly expressed in the renal tubules in mouse, rat, and human kidneys (38), and functions as a receptor for FGF-23 to promote renal phosphate excretion and to reduce serum levels of vitamin D. Klotho expression reduces as renal function declines, and so phosphate retention influences klotho expression (39). A high serum klotho level may decrease the severity of CKD and mineral bone disorder in maintenance of hemodialysis patients with low mineral density (40). Klotho also has various other functions that are unrelated to CKD progression, but that are related rather to human aging (41).

Vitamin D is known to control skeletal pathophysiology, regulating calcium and phosphorus and bone remodeling along with other calcium regulating hormones. Vitamin D deficiency has been associated with promoting atherosclerosis, vascular calcification and cardiovascular disease (42).

### Possible Measures to Reduce Phosphate Burden

*Is phosphate restriction harmful?* There is a concern that phosphate restriction may result in worse outcomes (43- 46). Previously, phosphate restriction placed more emphasis on protein restriction, which may lead to malnutrition, and an even worse prognosis, since malnutrition results in high mortality in hemodialysis patients (47). Therefore, we should instead consider reducing phosphate intake without restriction of protein consumption. So, it is important to reduce the phosphate-to-protein ratio. This lower ratio is

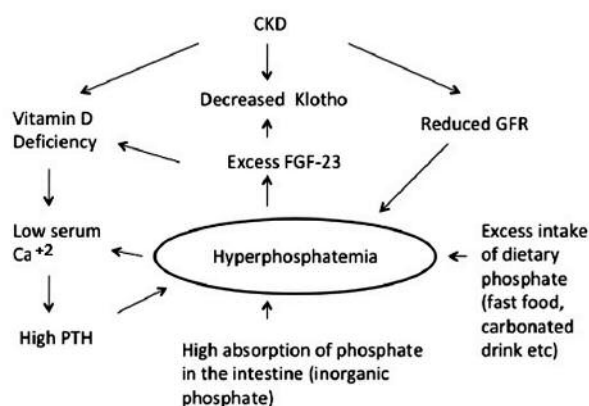


Figure 1. Mechanism of hyperphosphatemia in CKD patients.

crucial because a high ratio is related to increased mortality (48). These concerns can be minimized by reduction of phosphate additives instead restriction of the regular diet.

**Hidden phosphate intake from food additives.** Phosphate is one of the basic components of our daily food, and the phosphate content of food is primarily derived from protein (49). Nevertheless, in recent years, phosphate has been used as an additive in processed foods and beverages. These additives are used for many purposes *e.g.* as preservatives, acidifiers, curing agents, pH buffers, and emulsifying agents (50). Fast food, ready-to-eat packaged foods, cola and carbonated beverages, processed meats, in particular, often contain large amounts of phosphate additives. A recent study has showed that dairy products and cereals/grains containing inorganic phosphate additives significantly increase serum phosphorus concentrations despite them being less frequently consumed than phosphate additive-free foods (51).

Another important factor is food labeling. At present, it is not mandatory to report the amount of phosphate of the nutritional facts on the packaging, and so more phosphate is unknowingly consumed than can be estimated from nutritional databases. Therefore, it would be helpful to know what kind of food or beverages contain high amounts of phosphate.

**The quality of phosphate is a key.** The American groups have reported that dietary phosphorus intake increased between 2001 and 2014 in the USA. Grains were the largest dietary phosphorus source, followed by meats, and milk products. Soft drinks accounted for just 3.3% of total dietary phosphorus and were a minor contribution to total phosphorus intake (52). However, the inorganic phosphate compounds used as phosphate additives are absorbed extremely efficiently (90-100%) in the gut (53), while only

40-60% of organic phosphate originating from animal protein, and 20-50% of phytate-based organic phosphate from vegetables is absorbed (48). In addition, each food item has a different phosphate-to-protein ratio, which is potentially helpful information to enable a consumer to make better choices with respect to phosphate restriction (47). Indeed, both higher dietary food intake and higher phosphorus-to-protein ratios, estimated from food frequency questionnaires were associated with increased mortality in maintenance of hemodialysis patients (48). Additionally, restriction of phosphate levels by educating individuals to avoid phosphate additives and fast food has measurably reduced the level of phosphate in dialysis patients (54). A crossover trial to compare vegetarian and meat diets showed that one week of a vegetarian diet significantly reduced serum phosphate and FGF-23 levels while still containing the same amount of protein as a meat diet (55).

**Nutritional education.** Importantly, phosphate restriction is not the only restriction that CKD patients need to adhere to. In many cases, the patients become confused or overwhelmed, and personalized nutritional education is thus important (47). Instructions to patients could be simplified by asking them to avoid excess protein intake by consuming more foods of plant origin, and less fast foods, ready-to-eat meals and carbonated drinks. The use of functional foods such as low-phosphorus milk, cheese and soy sauce may provide more food choices for patients under these restrictions. Studies have shown that education significantly reduces serum phosphate levels in hemodialysis patients (56, 57). Contrary to these findings, however, it has been reported that nutritional education does not affect calcium-phosphate levels (58, 59). Thus, the effect of dietary education remains controversial, and further studies are needed in this area.

**Is there a lack of awareness, and how do we manage it?** We have previously documented the levels of awareness of dietary phosphate intake among future medical professionals such as medical and nursing students, and in patients undergoing hemodialysis using the same questionnaire, and have found that the majority of the students were unaware that fast food and soda drinks contain phosphate additives (60). By contrast, 46% of the patients undergoing hemodialysis were aware that a high-phosphate diet is harmful, although additionally they were unaware that fast food and soda drinks contain phosphate additives (24). When patients are introduced to maintenance hemodialysis, they are usually advised to reduce dietary phosphate intake and many are prescribed phosphate-lowering medications. In the study, most of the patients undergoing dialysis chose the answers "I want to get more information about phosphate" and "I want to reduce consumption of phosphate-containing food and drinks," after they had completed the questionnaire

(24). Their interest and willingness to change their dietary habits suggest that the intake of phosphate can be reduced if proper education programs are provided. Such programs could reduce total phosphate intake without requiring any pill burden or compromise in nutritional status.

## Conclusion

In order to reduce phosphate burden, awareness of its dietary sources is indispensable. Appropriate nutritional education may lead to the better control of phosphate in patients with CKD, and therefore to a better prognosis. It may also benefit the general population who has normal kidney function. Knowledge of phosphate additives, phosphate bioavailability and the phosphate-to-protein ratio would be helpful information in this respect. More research is obviously required in the future to produce reasonable clinical recommendations and better nutritional education. Finally, dietary phosphate toxicity is becoming a global health concern, and without measures in place to regulate optimal dietary intake, it is likely to induce harmful effects on the health of both diseased and healthy individuals (61).

## Conflicts of Interest

The Authors have no conflicts of interest to declare.

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